

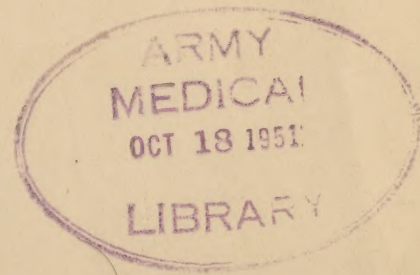
V2
A2
E67a

7/2

(DOCUMENT SECTION)

#2

Annual Report
of the
COMMISSION ON NEUROTROPIC VIRUS DISEASES
of the
Board for the Investigation and Control of
Influenza and Other Epidemic Diseases in the Army
covering the period May 1st, 1942, to April 30th, 1943
by
John R. Paul, M.D.
Director



PERSONNEL

During the past year the Commission has sustained the loss of one of its members - Dr. James D. Trask, whose death occurred on May 24th, 1942.

Three new members have been added to the Commission personnel; Dr. Murray Sanders of New York, Dr. Charles A. Janeway of Boston and Dr. Robert Ward of New Haven.

Two members, Dr. A. B. Sabin and Dr. M. Sanders, have joined the armed forces with the rank of Major in the Medical Corps. They will continue their work as members of the Commission after the period of military instruction has been terminated (presumably about April 15th).

REPORT OF ACTIVITIES

The work of the Commission during the past year is summarized under the headings of the various diseases with which the Commission has been concerned.

I. Epidemic Encephalitis. Experience of the past two summers (1941 and 1942) has failed to emphasize epidemic encephalitis as a military disease of numerical significance, for the number of cases in U. S. troops has been few. Nevertheless, because of its potentialities, the study of this disease, or group of diseases, continues to be the main concern of our Commission.

A. New Epidemiological Facts. From surveys conducted by Dr. W. McD. Hammon in Texas, Arizona, New Mexico, and the Yakima area in the state of Washington, the following important data are now available.*

I. Mosquitoes tested - collected during summer 1942

1. Texas - Lower Rio Grande Valley - no encephalitis 1942
horse or man (April - June)
(Severe drought - irrigation water with high salt content)
28,000 caught and frozen (6 genera, 20 species)
14,000 tested to date - no virus isolated
2. Arizona - Gila River Bend (Pinal County) - no encephalitis
1942 horse or man (June)
1,800 caught, frozen and tested - no virus isolated
3. Yakima Valley, Washington - 26-30 human cases, about 10
equine (July - September)
28,473 mosquitoes caught July 15-Sept. 15 (4 genera - 9 species)
24,751 tested to date - 48 strains of virus identified.

*Hammon, W. M., Encephalitis, J.A.M.A., 121, 560 (Feb. 20) 1943, and Hammon, W. M., Reeves, W. C., and Gray, M., Mosquito vectors and inapparent reservoirs of St. Louis and Western Equine Encephalitis viruses, Am. J. Public Health, 33, 201 (Mar.) 1943.

Mosquitoes Collected in the Yakima Valley, Washington July 15th
to September 15th, 1942 and the Results of Tests for Virus Content

Mosquito (Species)	No. tested	No. of Strains of Virus isolated	Viruses Identified Completely
<i>Culex tarsalis</i>	9,466	42	4-w.e.e., 3-s.l.e.
<i>Culex pipiens</i>	967	2	1-w.e.e., 1-s.l.e.
<i>Theobaldia inornata</i>	1,950	1	1-w.e.e.
<i>Theobaldia incidens</i>	62	0	-----
<i>Anopheles maculipennis</i> <i>freeborni</i>	4,496	3	0
<i>Anopheles punctipennis</i>	307	0	-----
<i>Aedes dorsalis</i>	4,866	0	-----
<i>Aedes vexans</i>	2,513	0	-----
<i>Aedes nigromaculus</i>	124	0	-----
Total	24,751	48	6-w.e.e., 4-s.l.e.

The isolation of 42 viruses from C. tarsalis offers ample confirmation of last year's finding of 8 strains of virus. Although only 7 of the 42 have been completely identified up to this time, tentative identification places 27 other strains as probably of the western equine type.

The isolation of one western equine and one St. Louis virus from Culex pipiens, and one western equine virus from Theobaldia inornata each represent first recorded isolations. The viruses isolated from Anopheles maculipennis have not been identified. From the feeding habits of this mosquito and data presented by others indicating that Anopheles quadrimaculatus can retain infection once acquired, this finding is not surprising. Its importance cannot be assessed at present.

The possibility exists of having isolated something other than western equine or St. Louis virus from the 48 strains obtained.

II. Experimental transmission

From 3 western areas, where encephalitis epidemics have occurred, 14 species of mosquitoes (from 5 genera) have been tested for ability to transmit western equine and St. Louis encephalitis viruses. Each virus was successfully transmitted by at least one species from each of 3 genera, Culex, Aedes and Theobaldia.

Culex tarsalis transmits both viruses, and transmission was effected with each virus by the bite of this species from one infected chicken or duck to another fowl after an extrinsic incubation period. Thus the vector role of this mosquito is proven and a possible natural vertebrate reservoir of virus demonstrated.

Since we previously demonstrated transmission of St. Louis virus by Culex pipiens, finding it infected in nature and suspected on epidemiologic grounds, establishes it as a vector of St. Louis virus.

Theobaldia inornata has just been proved capable of transmitting the western equine virus, so finding it infected with this virus establishes a second vector for the western equine virus. As yet there is no epidemiologic data to indicate that it plays an important role.

The role of mosquitoes as vectors in this disease now appears to be definitely established. Epidemiologic evidence also indicates that in the Yakima Valley there is a widespread inapparent reservoir of these viruses, which incriminates in particular domestic animals, especially fowls. It has been demonstrated that these animals, when suffering an inapparent experimental infection, have virus present in their blood.

The proportion of normal persons in the epidemic area in the Yakima Valley with antibodies to the St. Louis virus increases with length of

residence in the Valley (0-3 years = 9.1%; 12-20 years = 76.9%). Few were found with antibody to western equine virus.

From Texas is reported the first case of probable eastern equine infection in man occurring outside of the Massachusetts epidemic. The diagnosis is based on clinical history, a positive neutralization test on a convalescent specimen and the isolation of the virus from horses involved in the same epidemic.

Age and sex incidence and case fatality rates vary definitely in different areas, regardless as to which virus predominates. It would thus seem that the types of vectors may differ appreciably in different epidemic areas and the reservoir hosts may also differ greatly in such areas.

Conditions especially favorable to mosquito breeding were present at the time of epidemics, in all areas studied. In irrigated areas epidemics tended to recur annually; elsewhere sporadically as mosquito breeding conditions became favorable.

These observations serve to emphasize the need for mosquito control during epidemics. This should take the form of mosquito bite protection, larva control, residence in central urban areas, and animal zoning restrictions in peripheral urban areas.

Dr. Hammon believes that vaccination has a place in the control program inasmuch as vaccines against equine viruses are available, practical and probably effective. It is recommended that they should be used in selected groups of heavily exposed persons. Because of low encephalitis morbidity rates in most areas, vaccines are not recommended by Dr. Hammon for mass immunization programs.

B. Encephalitis Vaccines - Experimental Observations and Manufacture. It is not believed that any large scale vaccination program against

Western equine or St. Louis encephalitis is indicated for the Army or will be requested by the Army, but it is believed that the best available method of preparing such vaccines should be known, and the best available methods used for inoculating such vaccines should also be known. This information is to be placed in the hands of certain commercial houses so that in the event of a sudden demand for vaccine it could be produced quickly.

1. Equine Encephalomyelitis (Western) Vaccine. As mentioned in last year's report the Commission has followed the first large scale vaccination program against Western equine encephalitis which was conducted in Manitoba, Canada, under the direction of the local health department during May 1942. A report of our observations on this experiment which includes the antibody studies among vaccinees has been made to the Board.* This report records the fact that Lederle chick-embryo vaccine has been administered (2 doses - 1 cc. each 1 week apart) without bad effects to 3,000 farmers and that the neutralizing titer of antibodies in the vaccinees as tested by Major Sabin, 1 week, 2 weeks and 4 months after inoculation has been as recorded in Table 1.

Table 1. Development of Neutralizing Antibodies in 17 Vaccinees possessing none before Vaccination

Time after Vaccination	Neutralization Index		
	Positive %	Equivocal %	Negative %
1 week	12	6	82
2 weeks	100	0	0
4 months	81	7	12

* (a) Preliminary Report (No. 1) on the Vaccination of Man against Equine Encephalomyelitis (Western Type) by the Neurotropic Virus Disease Commission. Submitted to the Surgeon General's Office, August 1st, 1942.

(b) Preliminary Report (No. 2) on the Vaccination of Man against Equine Encephalomyelitis (Western Type). W.E.E. Neutralizing Antibodies in Sera obtained Before, 1 Week, 2 Weeks and 4 Months after Vaccination. In Preparation.

A similar, but comparative experiment on a somewhat smaller scale is now being conducted by Dr. Olitsky and Dr. Robert Ward in New York and Connecticut. It aims to determine the optimal vaccine which might be used in case of emergency. Two vaccines will be used: (a) Lederle's chick-embryo fluid vaccine and (b) Sharp and Dohme's allantoic fluid lyophilized vaccine. Comparative observations are being carried out in animals and in humans, and on the basis of these experiments recommendations will be made to the Board on or about July 1st, 1943, as to what type or types of vaccine might be used to advantage during epidemics.

2. St. Louis Encephalitis Vaccine. Chick-embryo has not proved to be a satisfactory means of propagating St. Louis virus for vaccine production. As a substitute, Major Sabin has developed a mouse brain vaccine against St. Louis encephalitis.* To date this vaccine has been inoculated into about 25 medical students without ill effects and the antibody titers produced by the inoculation have been found to be significant. Thanks to the Sharp and Dohme Company 1000 lyophilized units of this vaccine will be prepared for trial use as of the date of May 1st, 1943, and this material will be injected during May and June by Dr. Robert Ward into a large number of human subjects in an effort to determine the types of reactions which may be expected from this form of inoculation.

3. Japanese B Encephalitis Vaccine. Experiments similar to those with the St. Louis virus have also been carried out with Japanese B virus by Major Sabin. An experimental lyophilized mouse brain vaccine is being prepared also by the Sharp and Dohme Company which will be similarly tested in a large number of human subjects by Dr. Robert Ward during

* Sabin, A.B., Duffy, C.E., Warren, J., Ward, R., Peck, J.L., Jr., and Ruchman, I., Development of Noninfective Vaccines against St. Louis and Japanese B Types of Epidemic Encephalitis. Report of Basic Data. To be published.

See also Report by Major Sabin at the Meeting of the Neurotropic Virus Disease Commission held in New York City on January 22nd, 1943.

May and June, 1943.

C. Complement Fixation for Differentiating Viruses. In the laboratory of Dr. L. T. Webster a number of strains of encephalitis viruses have been subjected to comparative tests by the complement fixation method. This method has proved of particular value in the diagnosis of clinical cases. It has also proved of value in differentiating various strains of virus. In the latter connection it has been established in Dr. Webster's laboratory during the past year that there is a strong possibility that the tick-borne spring-summer virus encephalitis of man in the timber country of Russia and the tick-borne virus encephalitis of sheep in Scotland, known as louping-ill, may be caused by one and the same infectious agent (5). This discovery was made possible thanks to Dr. R. R. Parker of the U. S. Public Health Service, who supplied us with a strain of the Russian spring-summer encephalitis virus, and thanks also to Dr. Dyer of the U. S. Public Health Service.

Certain laboratories have experienced some difficulty in carrying out the complement fixation tests used in these experiments, and to circumvent one of these difficulties Dr. Webster has been active in developing a method whereby the antigen used in these tests can be prepared for him frozen and dried by the Sharp and Dohme Company so that they may be distributed to a few laboratories which are interested in this subject.*

D. Convalescent Serum Therapy. Experiments have been carried on in Dr. Olitsky's laboratory, which have dealt with the therapeutic aspect of hyperimmune serum in experimental encephalitis of the Western equine type (6).

II. Epidemic Keratoconjunctivitis. Serious outbreaks of this disease which have occurred in important defense plants in the East have made this condition

*See in Report by L. T. Webster at the Meeting of the Neurotropic Virus Disease Commission, held in New York City, January 22nd, 1943.

of importance to the Army. Problems with regard to this condition were assigned to the Neurotropic Virus Disease Commission in March 1942 and the work in connection with epidemiological and laboratory investigations has been carried out by Major Murray Sanders. Major Sanders has isolated an infectious agent from patients suffering with this condition, which has been passed successfully in mice and in tissue culture (1)(2). Its identity has been partially confirmed by the inoculation of the human eye in a volunteer with the resulting production of clinical epidemic keratoconjunctivitis. The neutralization tests which may have considerable value in the diagnosis of clinical cases have been devised. See bibliography.

Major Sanders has been instrumental in finding out that the spread of this condition has taken place through physicians' offices (3) and through the eye dispensary of certain industrial plants. The virus which he has isolated has been shown to be stable in the usual solutions used in the ophthalmological dispensary. The disease has been reported on the West coast in the winter of early 1942 and in the East at Schenectady, New York, Buffalo, N.Y., also Connecticut, Michigan, Illinois, Maryland, Virginia, Texas, and New Jersey. Major Sanders has suggested the use of convalescent serum in the treatment of this condition (4).

Part of the work in connection with this disease has been that of spreading information, and for this several meetings have been held which have been organized in part by the Office of the Surgeon General. These meetings have been held in New York City and in the Middle West. Partially as a result of this activity the disease has now been made reportable in several states in this country including New York and Michigan. It has also been added to the manual on the control of communicable diseases sponsored jointly by the Public Health Service and the American Public Health Association.

III. Lymphocytic Choriomeningitis. Preliminary reports of the experience in the Army during the past two years (1941-42, 1942-43) have failed to indicate that lymphocytic choriomeningitis is a disease of much military importance. In 1942 about 25 cases were listed in the Army records which were available to this Commission, but in spite of this small number, laboratory evidence has been assembled at the Army Medical School to indicate that the disease deserves further investigation.* For this reason a laboratory for the study of lymphocytic choriomeningitis was established by the Neurotropic Virus Disease Commission in November 1942. It is now under the direction of Dr. Charles A. Janeway at the Children's Hospital in Boston.

IV. Poliomyelitis. Poliomyelitis cases in the Army during 1942 were few in number; only about 16 cases were reported to the Commission. This low incidence is in keeping with the experience of the Army during the previous year. Nevertheless, in December 1942 and in January 1943 the Commission was called upon to investigate a poliomyelitis epidemic which occurred in San Antonio, Texas. Three cases, one of them fatal, occurred among soldiers, but many cases occurred among the families of officers and men posted in that area. A report of the investigation carried on by the Commission in this area during the epidemic, has been made to the Surgeon General's Office.** Several strains of virus were isolated from material collected during the epidemic, including stools from clinical cases, the spinal cord of a fatal case and a sample of flies collected in the City of San Antonio.

It was our experience in this epidemic that poliomyelitis may indirectly become a military problem when it appears in the families of

*Report by Lt. Col. H. Plotz made at the Meeting of the Neurotropic Virus Disease Commission held in New York City, October 8th, 1942.

**Paul, J. R., Preliminary Report on the Poliomyelitis Epidemic in San Antonio, Texas (September - December 1942) submitted by the Neurotropic Virus Disease Commission to the Surgeon General's Office, February 1st, 1943.

officers and men living on a military post. The degree of apprehension which involves families who are living under common circumstances may be great in such an epidemic.

Another aspect of situations of this type which involve the Army should also be mentioned, namely: the facilities which the Army can offer to anyone investigating epidemiological aspects of this disease in a military area may be exceptionally good. Facilities for the collection of specimens (including those of insects) through the use of trained entomologists, sanitary engineers and other types of personnel are such, that the military epidemic of poliomyelitis represents a very unusual opportunity for investigation.

V. "Fort Bragg Fever". During September 1942 one of the members of the Commission was called upon to assist in the study of an acute febrile epidemic disease which occurred among certain military units stationed at Fort Bragg, North Carolina. Other members of this group assigned to investigate the condition included, Dr. Norman H. Topping of the U. S. Public Health Service and Major C. B. Philip of the Army Medical School. Preliminary and final reports of this investigation have been submitted to the Surgeon General's Office.* In brief, these reports indicate that this disease was a clinical entity which does not resemble any of the well-recognized diseases known today. It was quite similar to a condition recorded in Georgia but not described in published form by Dr. C. D. Bowdoin (Director, Division Preventable Diseases, Georgia State Department of Health) during the summer of 1940. This condition, which was characterized by about 4 or 5 days of acute fever in many instances was

*Topping, N.H., Philip, C.B., Maj. Sn.C., and Paul, J.R., Preliminary Report of the Commission for the Study of an Unidentified Disease at Fort Bragg, N.C. (September 3 - September 11, 1942), submitted to the Office of the Surgeon General, October 15th, 1942.

Ibid., Final Report, submitted April 15th, 1943.

accompanied by a maculo papular rash which for the most part, was limited to the lower extremities, also had as its characteristic a minor leucopenia and splenomegaly.

The infectious agent responsible for this disease was not identified.

VI. Expedition to North Africa. In October 1942 steps were taken to determine whether more information could be obtained about poliomyelitis and encephalitis cases which were known to have existed among British troops stationed in the Near East. Plans for this investigation did not materialize, but in February 1943 it was decided that other epidemic problems, including those of encephalitis, sandfly fever and epidemic jaundice might also warrant investigation by a group of men who would be sent for this purpose to that particular area. Such a group has been organized under the Neurotropic Virus Disease Commission and it now consists of Major A. B. Sabin, M.C., Major C. B. Philip, Sn.C. (entomologist) and Dr. J. R. Paul. This group is to carry out a survey in the areas in which the disease is present, and to establish a laboratory in the Middle East if it seems wise to do so. The National Foundation for Infantile Paralysis has made a generous grant of \$15,000 to assist in carrying this work forward during the first three months that the expedition is in the field.

Respectfully submitted,

(Signed) John R. Paul

John R. Paul, M.D.
Director

April 17, 1943

Publications under the Commission on Neurotropic Virus Diseases

May 1942 - May 1943

1. Sanders, M., Epidemic keratoconjunctivitis ("shipyard conjunctivitis")
1. Isolation of a virus, Arch. Ophthal., 28, 581 (Oct.) 1942.
2. Sanders, M., and Alexander, R.C., Epidemic keratoconjunctivitis. 1. Iso-
lation and identification of a filtrable virus, J. Exper. Med., 77, 71
(Jan.) 1943.
3. Sanders, M., Gulliver, S.B., Dersheimer, L.L., and Alexander, R.C.,
Epidemic keratoconjunctivitis, J.A.M.A., 121, 250 (Jan.23) 1943.
4. Braley, A.E., and Sanders, M., Epidemic keratoconjunctivitis, J.A.M.A.
121, 999 (Mar.22) 1943.
5. Casals, J., and Webster, L.T., Close relation between Russian spring-
summer encephalitis and louping-ill viruses, Science, 97, 246 (Mar.12)
1943.
6. Olitsky, P.K., Schlesinger, R., Walter, R., and Morgan, Isabel M.,
Induced resistance of the central nervous system to experimental infec-
tion with equine encephalomyelitis virus. II. Serotherapy in Western
virus infection, J. Exper. Med., 77, 375 (Apr.) 1943.